REMARKS/ARGUMENTS

Claims 1-80 are pending claims. Claims 30 and 47-64 are currently under consideration. Applicants will cancel non-elected claims upon indication of allowable subject matter. Applicants add new claims 81-86. Support for the subject matter of these claims is found throughout the specification. No new matter has been entered. Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the Office Action.

1. Applicants note with appreciation that the response filed March 20, 2003 has been entered.

2. The declaration filed under 37 CFR 1.63 on January 3, 2002 is objected to as defective because it does not identify the provisional application that this application claims priority. Applicants traverse this objection. Neither the regulation nor the MPEP requires that a declaration identify the U. S. provisional application to which an application claims priority. See 37 CFR § 1.63 and MPEP § 602. Furthermore, as acknowledged by the Examiner, the application data sheet identifies the relevant provisional application. In a telephonic interview on August 18, 2003, the Examiner agreed to withdraw the objection. Written withdrawal of this objection is respectfully requested.

3. The abstract is objected to due to an informality. Specifically, it is objected to because the word "said" appeared twice in the abstract. In response, Applicants have amended the abstract to obviate the objection.

4. Claims 30, 47 and 52 are objected to due to several informalities. Applicants have amended the claims accordingly to obviate the objections. Applicants submit that these amendments do not narrow the scope of the claims.

5. Claims 30 and 47-64 are rejected under 35 U.S.C. §112, first paragraph for allegedly containing subject matter which was not described in the specification in such a way as to enable

one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Specifically, the Examiner based the rejection on the assertion that the two types of transgenic mice, the muFcRn -/-, and the muFcRn -/-, huFcRn + mice, cannot be routinely and reproducibly made in light of the state of art of transgenic technology at the time the subject application was filed. Applicants disagree. The technologies for making knockout and transgenic mice were routine at the time of the filing of the present application, which is November 6, 2001. In October 2001, researchers who pioneered the knockout technologies were awarded the prestigious Lasker Award. The Press Release from the Lasker Foundation stated that targeting a specific gene to generate a knockout mouse is "a standard maneuver". See Lasker Foundation Press Release, October 2001, "Today, hitting a bull's-eye is a standard maneuver." available at http://www.laskerfoundation.org/awards/library/2001b_cit.shtml. A copy of the Press Release is enclosed with this Reply as Exhibit 1. That the technologies for making knockout and transgenic mice were routine at the time of filing is clear from the fact that, by October 2001, over 4000 genetically engineered mice had been generated, according to the Lasker Foundation. In fact, the Examiner acknowledged that "the technique of making transgenic and knock out mice has become routine in the relevant art". See Office Action, page 6, line 16-17.

Applicants described, in the subject application, all of the materials and procedures needed to produce the two types of transgenic mice used in the claimed methods. Applicants have disclosed a vector successfully used to create the muFcRn -/- knockout mouse and a screening strategy to select for the correct integration event (See Figure 1 and 2). Applicants further disclosed the making of a muFcRn -/- mouse by standard gene targeting technology and the verification of the muFcRn disruption by real-time quantitative PCR analysis of muFcRn transcript. See Specification, pages 41-43. The making of transgenic mice carrying human FcRn transgene is routine as well, especially given the extensive guidance provided in the specification. See Specification, page 35, and 44-45.

The Examiner stated that the genotype and phenotype of transgenic animals "varies significantly depending on the *genes being manipulated* and the animals being used". Office

Action, page 6, emphasis added. Citing the Linder and Nebert references, the Examiner indicated that different genetic backgrounds of the animals influence the phenotype of the transgenic animals. This argument is inapplicable to the present application for two reasons. First, contrary to what the Examiner suggested, the "genes being manipulated" in the present application are not variable. Making the transgenic mice of the present invention only involves the mouse FcRn gene and the human FcRn gene, both of which were known at the time of filing of the present application. Second, the assertion that genetic background may affect the phenotype of transgenic animals by no means leads to the conclusion that the transgenic mice of the present invention cannot be routinely and reproducibly made. The practice of the methods of claims 30 and 47-64 relies on the disruption of the mouse FcRn gene in the muFcRn -/- knockout mouse and expression of the human FcRn gene, both of which can be verified according to the guidance provided in the present application. The disruption of the mouse FcRn gene can be further verified by assaying for IgG clearance from the mouse serum. As Applicants showed in the present application, the muFcRn -/- mouse has substantially increased IgG clearance from the serum than a wild-type mouse. See, for example, Specification, page 31, Table 1 and Figure 5. Applicants also teach how to produce the desired transgenic mouse, which expresses the human FcRn transgene. This was achieved by producing a number of transgenic lines and selecting mice which express huFcRn by a combination of non-quantitative PCR, quantitative RT-PCR and real-time quantitative PCR analysis. See, for example, Specification, page 35, 44-46 and Figure 6. Thus, with the teachings of the present application, one of ordinary skill in the art could have generated the muFcRn -/- and muFcRn -/-, huFcRn transgenic mice in different genetic backgrounds and verified the desired genotype of the knockout allele and the desired expression of the human transgene according to the methods detailed in the present application.

The Examiner further states that making transgenic animals is unpredictable because the expression of the transgene varies, depending on where the transgene integrates into the genome. The Examiner cites Mullins and Mullins, Logan and Sharma in support of this position. In the context of making transgenic mice, the position effect could be, and had been, routinely addressed by producing a number of transgenic mouse lines from different cell lines and selecting the ones with desired transgene expression at the time of the filing of the present application. Moreover, both the Mullins reference and the Logan reference fail to support the Examiner's argument because both discuss transgenic technology in the context of animals other

than mouse. The Mullins reference is a review of "the application of transgenic technology to *nonmurine* species" (See Mullins and Mullins, page 1557, at the end of the first paragraph. (Emphasis added)). The Logan and Sharma reference, entitled "Potential Use of Genetically Modified Pigs as Organ Donors for Transplantation into Humans", discusses transgenic technology in the context of genetically modified pigs. It is known that transgenic/knockout technology is much more well-developed in mouse than in other mammalian species. Discussions about transgenic technology in other mammalian species are not applicable to mice.

The process of generating transgenic mice used in the present invention does not require undue experimentation. The standard for what constitutes undue experimentation is not a quantitative one. Rather, "a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed". MPEP 2164.06. In the present case, Applicants have provided ample guidance with regard to how to screen for the correct genotype of an muFcRn knockout and how to screen for the desired expression of the human FcRn transgene in a transgenic mouse, as discussed above. In support of this position, Applicants submit a declaration under 35 §U.S.C. 1.132 by Dr. Roopenian, enclosed with this Reply as Exhibit 2.

Furthermore, the position of Applicants is consistent with the established practice of the Patent Office, which, to date, has issued numerous patents with claims directed to transgenic mice and/or methods of using the mice. For example, U.S. Patent No. 6,566,581 (the '581 patent), filed on June 10, 1999 and issued on May 20, 2003, has claims directed to transgenic mouse (claims 1-3) and claims directed to methods of using the transgenic mouse (claims 4-7). The '581 patent disclosed only vectors used to generate the desired knockout mice, the selection and screening strategy, and confirmation data of the knockout mouse created, all of which were disclosed by Applicants in the present application. A copy of the '581 patent is enclosed with this Reply as Exhibit 3.

Taken together, Applicants submit that the specification and the state of the art enable one of ordinary skill in the art to make the transgenic mice used in the present invention. Accordingly, reconsideration and withdrawal of this rejection is respectfully requested.

6. Claims 47-64 are additionally rejected under 35 U.S.C. §112, first paragraph because the Examiner deemed the use of "a trackable composition" attached to a candidate agent for FcRn-mediated drug delivery as being non-enabled. Applicants traverse this rejection.

Applicants submit that the identity of such trackable composition and their uses are well known in the art and need not be described in the specification. The specification explains what a trackable composition is, as correctly recognized by the Examiner, by stating that "[t]he identity of the trackable composition may produce a physiological effect on mouse function or may simply be an easily detectable molecule, (e.g., through enzymatic activity or recognition of or as an antigen)" (Specification, page 23, lines 30-35). A person of ordinary skill in the art reading the claims in light of the specification will understand that the trackable composition of the present application may be attached to a candidate agent to facilitate detection/tracking of the candidate agent. Trackable compositions include reporters or detectable labels. Examples of such trackable compositions and their uses were abundant in the scientific literature at the time the subject application was filed. For instance, Hadjantonakis and Nagy, in a review entitled "The Color of Mice: in the Light of GFP-variant Reporters", discuss the use of GFP and its variants in transgenic and knockout mice. See Hadjantonakis and Nagy, *Histochem Cell Biol.* 115: 49-58 (2001), published online: December 21, 2000. A copy of this reference is enclosed with this Reply as Exhibit 4. Other examples of trackable compositions include LacZ, human placental alkaline phosphotase, luciferase and glutathio s transferase (GST). A person of ordinary skill in the art reading the claims in light of the specification will understand that trackable compositions may also include, for example, antigens that are readily detected by a range of methods, including ELISA and radio labeling. Relevant references were incorporated in the specification. See, for example, Junghans and Anderson, Proc. Natl. Sci. U S A 93: 5512-6 (1996), which was incorporated in the present specification. See Specification, page 30, lines 6-7 and line 16. A copy of the Junghans reference is enclosed with this Reply as Exhibit 5. Trackable compositions also encompass molecules that produce physiological effects on mouse function. Such physiological effects include, for example, shrinking of a tumor, changes in red blood cell counts, or the rate of clearance from serum of a particular protein. As used in the present application, a candidate agent can be formulated with a trackable composition. See

Specification, page 23, line 11-13. For example, the candidate agent itself may be trackable. In fact, the specification provides such an example: IgG is an agent that promote FcRn mediated drug stabilization and it can be tracked by ELISA method. See Exemplification section of the Specification, page 43, lines 24-31. Alternatively, trackable compositions can also be attached to a candidate agent using standard molecular biology techniques. Applicants submit that a person with ordinary skill in the art reading the specification would have been able to carry out the invention without undue experimentation. Applicants' position is further supported by MPEP, which specifically states that "a patent need not teach, and preferably omits, what is well known in the art". In re Buchner, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), cert. denied, 480 U.S. 947 (1987). See MPEP 2164.01.

In making the rejection, the Examiner also pointed to the fact that no example of the trackable composition was provided. Compliance with the enablement requirement does not turn on whether an example, working or prophetic, is disclosed. See MPEP 2164.02. Moreover, Applicants has given working examples for a FcRn-mediated drug delivery or drug stability agent formulated with a trackable composition in the present application. The use of IgG throughout the application is such an example. IgG, through its binding to FcRn, is an agent for FcRn-mediated drug delivery and a FcRn-mediated drug stability. At the same time, IgG can be detected with a range of methods such as ELISA used in the present application. Thus, IgG is an example of an agent formulated with a trackable composition. See, for example, measuring absorption of maternal IgG by neonatal mice and IgG clearance assays described on page 43 of the specification.

Therefore, Applicants maintain that the specification and the state of the art enable the scope of the claims. Accordingly, reconsideration and withdrawal of this rejection is respectfully requested.

7. Claim 52 is additionally rejected under 35 U.S.C. §112, first paragraph for allegedly failing to "teach how and whether it is feasible to obtain blood from the fetus of a mouse". Applicants traverse this rejection. At the time of filing of the present application, it was feasible for one with ordinary skill in the art to obtain blood from the fetus of a mouse. See, for example,

Applyby and Catty, J. Reprod. Immunol. 5: 203-13 (1983). A copy of the Applyby reference is enclosed with this Reply as Exhibit 6.

8. Claims 49 and 54 are rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite due to the use of the phrase "such as" in the claims. Applicants have amended the claims to delete the phrase "such as" to obviate the rejections.

Claims 60 and 64 are rejected for lack of antecedent basis for the limitation "the engineered molecule" in the claims. Applicants have amended claims 60 and 64 to obviate the rejections.

Claim 61 is rejected under 35 U.S.C. §112, second paragraph, as allegedly being vague and indefinite, and for lack of antecedent basis for the limitation "the agent, formulate without the candidate agent". Applicants have amended claim 61 to obviate these rejections. In making the rejection, the Examiner alleged that it is unclear "how the formulation is 'trackable'". Applicants traverse this rejection to the extent that it is maintained in light of the amended claim 61. The word "trackable", as used in claim 61, has the same meaning as it is used in the phrase "trackable composition", defined on page 23 of the Specification. Applicants submit that a person of ordinary skill in the art reading claim 61 and the Specification will understand how to carry out the method of claim 61.

Applicants submit that these amendments do not narrow the scope of the claims. In light of the amendments, reconsideration and withdrawal of the rejections are respectfully requested.

9. Claims 30 and 47-64 have been found to be free of cited prior art of record.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants submit that the pending claims are in condition for allowance. Early and favorable reconsideration is respectfully solicited. The Examiner is invited to contact the undersigned at 617-951-7000. A petition for a two-month extension of time, with authorization to charge the required fee to Deposit Account No. 18-1945, Order No. JMY-P01-002, is being filed concurrently. If a further extension is required, Applicants' attorney respectfully requests that such extension be granted and any fee required be charged to Deposit Account No. 18-1945, Order No. JMY-P01-002.

Respectfully Submitted,

Date: September 15, 2003

Weishi Li
Reg. No. 53, 217

Customer No: 28120
Docketing Specialist
Ropes & Gray
One International Place
Boston, MA 02110
Phone: 617-951-7000
Fax: 617-951-7050